Published in final edited form as:

Proc IEEE Int Symp Biomed Imaging. 2017 ; 2017: 961–965. doi:10.1109/ISBI.2017.7950675.

A COMPARISON OF NETWORK DEFINITIONS FOR DETECTING SEX DIFFERENCES IN BRAIN CONNECTIVITY USING SUPPORT VECTOR MACHINES

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Abstract

Human brain connectomics is a rapidly evolving area of research, using various methods to define connections or interactions between pairs of regions. Here we evaluate how the choice of (1) regions of interest, (2) definitions of a connection, and (3) normalization of connection weights to total brain connectivity and region size, affect our calculation of the structural connectome. Sex differences in the structural connectome have been established previously. We study how choices in reconstruction of the connectome affect our ability to classify subjects by sex using a support vector machine (SVM) classifier. The use of cluster-based regions led to higher accuracy in sex classification, compared to atlas-based regions. Sex classification was more accurate when based on finer cortical partitions and when using dilations of regions of interest prior to computing brain networks.

Index Terms

brain connectivity; networks; nodal; classification; atlas; cluster

1. INTRODUCTION

Human brain connectivity is highly complex, and a surge of interest in modeling brain networks has led to wide variety of methods to define them. Here we seek to understand (1) which aspects of brain connectivity tend to differ, at least on average, by sex, and (2) how the detection of sex differences depends on choices made in network reconstruction and analysis [1, 2, 3, 4]. Sex has subtle and diffuse effects on brain connectivity that are not well understood. As well as the neurobiological interest in defining connectivity features that tend to differ by sex, here we treated it as a relatively challenging classification problem, to see how the results depend on analytic choices made in defining brain networks.

Diffusion MRI is now widely used to image the brain's white matter microstructure. Tractography algorithms can compute sets of fibers that follow major white matter pathways that interconnect brain regions; these pathways can be organized into brain networks, and network properties can be computed to describe high-level patterns of organization in the brain.

It is unclear which techniques and methods are best for a given classification problem, and some groups have developed adaptive methods that adjust network definitions to boost discrimination accuracy or heritability in independent test data [5]. The most appropriate analysis methods may also depend on the scan acquisition protocol, the tractography algorithm used and post-processing methods such as high-order singular value decomposition [2, 6, 7, 8]. For instance, the ability of the structural connectome to reflect the underlying anatomy is affected by the spatial, angular, and spectral resolution of the scanning protocol [9], the field strength [10] and duration of the scan, and how well post-processing techniques suppress noise or adjust for distortion or artifacts. Network models of connectivity and their properties also depend on the protocols to define regions or nodes in these connectivity networks, how connectivity strengths are normalized based on overall counts of detected fibers or the volumes or areas of the regions they interconnect, and how we define the presence of a connection between pair of regions.

Here we investigated several logical choices in the analyses of structural connectomes to see how they affected our ability to classify sex differences in a set of 410 healthy young adults [11, 12].

2. METHODS

2.1. Subjects

We analyzed T1-weighted (T1w) structural brain MRI scans and high angular resolution diffusion images in 410 unrelated individuals (HARDI; from 161 men, 249 women; mean age 21.2 ± 4.0 years when scanned) as part of the Queensland Twin IMaging (QTIM) study, a neuroimaging and genetic study of young, healthy adult twins and their family members.

2.2. Acquisition

High resolution T1-weighted structural scans were acquired with an inversion recovery rapid gradient echo sequence (TI/TR/TE = 700/1500/3.35 ms; 240 mm FOV; 256×256 acquisition matrix; $0.98 \times 0.98 \times 0.94$ mm³ voxels/0 mm gap). HARDI scans were acquired with single-shot echo planar imaging with twice-refocused spin echo sequence to minimize eddy-current distortions (23 cm FOV; TR/TE 6090/91.7 ms; 128×128 acquisition matrix). 105 images were acquired per subject: 11 T2-weighted b_0 images and 94 diffusion-weighted images ($b=1149$ s/mm²) with gradient directions evenly distributed on a hemisphere in the q -space. Each 3D volume consisted of 55 2-mm thick axial slices with no gap, and 1.79×1.79 mm² in-plane resolution.

2.3. Data Processing

HARDI images were corrected for motion and eddy current distortions in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). For each subject, b_0 images were registered to their respective T1w images using boundary-based registration with FSL FLIRT. The inverse transformation was then applied to the T1w image. Now in diffusion space, b_0 images were nonlinearly transformed to the T1w brains using a SyN mutual information registration in ANTs, which was restricted to the expected direction of distortion [13]. Finally, HARDI data were linearly aligned to the MNI152 2-mm template brain and b -vectors were rotated accordingly. *DiPy* (<http://nipy.org/dipy/>) was used to compute deterministic streamline tractography (with the “LocalTracking” module). Fiber orientation distributions were modeled at each voxel. Streamlines were seeded 3 times per voxel in a white matter mask. Streamline tracking proceeded in 0.5 mm steps using a probability mass function (“MaximumDirectionGetter” module). A representative example for one subject’s computed tractography is shown in Figure 1.

Anatomical MRI data were pre-processed with FreeSurfer (version 5.3; <http://surfer.nmr.mgh.harvard.edu/>) to create cortical segmentations in two ways:

1. **Atlas-Based.** A standard anatomical partition was generated, composed of 68 nodes (34 per hemisphere) based on the Desikan-Killiany atlas from FreeSurfer.
2. **Cluster-Based.** We computed a series of increasingly refined connectivity networks based on clustering the FreeSurfer white matter surface atlas using k-means clustering. The result from the clustering is k equally sized regions on the surface derived by comparing points based on their Euclidean distance from one another. This atlas was matched to each subject in our dataset to obtain a correspondence in each region across the cohort. We computed 10 different resolutions or 10 different values of k in the clustering algorithm: 100 clusters (low resolution) up to 1000 clusters (high resolution), in increments of 100. This allowed us to create connectivity networks with more nodes while ensuring correspondences among nodes across the dataset. Prior studies developed distinct strategies to build the connectome with multiple scales of parcellation, using high resolutions such as 998- and 4000-node parcellations [14, 15]. Here, we assess whether an individual or set of resolutions/scales offers distinct advantages in identifying features that assist sex classification.

Both atlas-based and cluster-based sets of nodes were dilated in FreeSurfer space to ensure intersection of cortical regions with streamlines extracted from the white matter [1] (Figure 2).

For each subject, their brain image was linearly aligned (6 degrees of freedom) to MNI152 1-mm template brain space and downsampled to 2-mm isotropic voxels. Using this transformation, we linearly aligned cortical labels to this brain image using nearest neighbour interpolation to avoid intermixing of labels.

2.4. Structural Connectome

We compared two ways of constructing the structural connectomes based on tractography along with a set of ROIs at the gray-white matter boundary. The weight of an edge in the connectome between two different regions was defined to be proportional to the number of fibers connecting those regions. We studied two definitions of fiber connectivity. The first approach defined a connection as present between ROIs if any point on the fiber intersected both regions (Figure 3A). This definition also allows there to be multi-region fibers (Figure 3B)—meaning a single fiber could connect more than two regions together and is counted as multiple fibers in the resulting network representation, e.g., if a single fiber passed through 4 regions, it would be counted as 6 different connections in the resulting connectome [16]. Hundreds of studies have employed this definition in brain connectomics with the obvious limitation of “diluting” the connectome. The second approach restricted connectivity based on only the endpoints of each fiber such that a single fiber could connect at most two regions and that fiber is counted only once in the final connectome (two-region or endpoint fibers; Figure 3C) [17, 18, 19, 20]. Here, we hypothesized that using two-region (endpoint) fibers would be more informative by avoiding the “overcounting” of connections and focusing on real axonal pathways in the connectome. Our two definitions are compared in Figure 3.

For these two types of networks we studied 3 normalization schemes: (1) the raw networks—where a connection represents the number of streamlines between two regions; (2) the “count normalized” networks that normalize the connections by the total number of streamlines detected in a participant, and (3) the “count and volume normalized” networks—which involves normalizing all connections based on the total streamline count and the combined volume of the two connected regions. The motivation to normalize brain networks is to correct for inter-subject variability in cortical (gray matter) volume because this volume constrains the total number of streamlines per node [21, 22]. In addition, we evaluated whether including or leaving out intra-node connectivity changed classification results.

2.5. Classification

Support Vector Machines (SVM) are a classification approach to learn a binary decision boundary based on training data. We used linear kernel SVMs as the classification function and can be interpreted as representing a hyperplane in d -dimensional feature space, where d is the number of variables or features for each participant. In our case the number of features corresponds to the number of unique connections in a connectivity network for a set number of nodes.

2.6. Classification Performance

To evaluate the classifier we used 10-times repeated stratified 10-fold cross-validation, which involves repeatedly learning parameters from training data and evaluating the model on independent test data; the approach offers a tradeoff between bias and variance in our performance estimates by balancing the size of the testing and training subsets of data [23]. To account for the differences in our class sizes, we quantified performance using balanced accuracy (the mean of sensitivity and specificity), which equally weights the accuracy (or percent of correctly classified samples averaged over all test sets) on each class [24].

3. RESULTS

Classification of sex using SVM was performed for each combination of the following parameters: 11 resolutions (10 cluster based sets of nodes/regions and 1 atlas based), 2 fiber connectivity interpretations (multi-region and two-region), 3 normalization techniques (raw, “count normalized”, and “count and volume normalized”), 5 cortical label dilations (0–4 dilations), and intra-node inclusion or exclusion, for a total of 660 possibilities.

First, we compared intra-node connectivity inclusion vs. exclusion. Inclusion yielded higher accuracy (0.722 ± 0.072 vs. 0.710 ± 0.075) and sensitivity (0.537 ± 0.178 vs. 0.512 ± 0.189) performance measures for every combination. Inclusion generally resulted in lower specificity (0.906 ± 0.053 vs. 0.908 ± 0.057 ; Figure 4A; *only accuracy shown*). Next, we tested the effect of ROI dilation to determine the granularity of white matter fiber groups and their interaction with gray matter. Here, we tested a maximum of 4 dilations, as this prescribed cortical labels within a reasonable anatomical boundary and also limited the effect of head size on classification. Increasing dilation improved sex classification accuracy (0.749 ± 0.052 vs. 0.647 ± 0.080) with a higher degree of sensitivity (0.603 ± 0.138 vs. 0.370 ± 0.138) for every combination (Figure 4B; *only accuracy shown*). Although dilations improved sensitivity, specificity was severely impaired (0.896 ± 0.047 vs. 0.925 ± 0.067), which is consistent with findings of a recent study [25]. We then compared the various resolutions with sex classification and established two main patterns: (1) lower resolutions enhanced sex classification performance for two-region (endpoint) fiber based connectomes, (2) normalization schemes favored two-region (endpoint) fiber based connectomes at lower resolutions and multi-region fiber based connectomes at higher resolutions. In addition, we arrived at three conclusions: (1) sex classification performance begins to decline at resolutions of > 300 clusters, (2) based on accuracy and sensitivity, the optimal normalization technique was “count and volume normalized”, and (3) specificity improved with increasing resolution and favored two-region (endpoint) fiber based connectomes for each normalization technique (Figure 4C; *only accuracy shown*).

So far, we found that accuracy was boosted with intra-nodal connectivity, increased dilations, and count and volume normalization. We then compared the optimal cluster-based connectome with the optimal atlas-based connectome (Figure 4D; *only accuracy shown*). The cluster-based connectome outperformed the atlas-based connectome. Accuracy, sensitivity, and specificity performance measures for these two connectomes are summarized in Table 1.

4. CONCLUSIONS

We evaluated structural connectomes from 410 participants using SVM to classify sex. Cluster-based nodes outperformed atlas-based nodes for classification. This was true for different means of defining connectivity, normalization schemes, and whether intra-node connectivity was included. Higher resolution connectomes may boost the power of connectivity studies by identifying arrangements of connections that may reflect the underlying biological patterns better than those based on standard gyrus-based anatomic

atlases. As the field of human brain connectomics evolves, relationships between analysis choices and the sensitivity of the methods are important to consider.

Acknowledgments

This work was supported in part by *NIH Big Data to Knowledge* (BD2K) Center of Excellence grant U54 EB020403, funded by a cross-NIH consortium.

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Fig. 1. Tractography

A superior view displaying tractography for a representative participant's brain with 1000 clusters (described later) illustrated in transparent pink (*left*). The same dilated clusters are in solid, random colors to illustrate their shapes and demarcations between adjacent clusters (*right*).

Fig. 2. Successive dilations of cluster-based nodes
From top-left to bottom-right, 0–4 dilations of 1000 clusters.

Fig. 3. Comparison between multi-region and two-region (endpoint) fiber based approaches
Multi-region fibers count all connection possibilities for each streamline, whereas two-region (endpoint) fibers include only one connection per streamline.

Fig. 4. Summary of sex classification accuracy performance

mr: multi-region; *ep*: two-region (endpoint); *cn*: “count normalized”; *cvn*: “count and volume normalized” **A.** Sex classification accuracy was compared for all possible connectome parameter combinations for intra-node connectivity inclusion vs. exclusion. Classification improved when the diagonal was included. **B.** Dilations show a greater advantage to two-region (endpoint) fiber based connectomes than multi-region fiber based connectomes, where sex classification accuracy was more stable. **C.** Two-region (endpoint) fiber based connectomes favored low resolutions (100–300 clusters). At high resolutions (>300 clusters), sex classification performance begins to decline in two-region (endpoint) fiber based connectomes. In contrast, sex classification performance in multi-region fiber based connectomes was more robust to differences in resolution. **D.** Cluster-based classification outperformed atlas-based classification.

Table 1

Summary of Classifier Metrics

Method	Accuracy	Sensitivity	Specificity
CB	0.847 ± 0.006	0.801 ± 0.011	0.892 ± 0.006
AB	0.817 ± 0.011	0.783 ± 0.022	0.851 ± 0.004

CB: Cluster-based; AB: Atlas-based